Reaction of 6 with Sodium 2-Benzothiazolethiolate. To a solution of **6** (72 mg, 0.15 mmol) in acetone (2 mL) was added sodium 2-benzothiazolethiolate (62 mg, 0.33 mmol) at 0–5 °C. After being stirred for 1 h at this temperature the reaction mixture was worked up and chromatographed (SiO_2; hexane–AcOEt, 5:1) to give **7a** (75 mg, 68%) as a colorless foam: IR ($CHCl_3$) 1775, 1717, 1609, 1452 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.74 (br s, 2 H), 4.33 (br s, 2 H), 4.68 (d, 1 H, J = 13.5 Hz), 4.79 (d, 1 H, J = 13.5 Hz), 5.22 (s, 2 H), 5.79 (d, 1 H, J = 4.5 Hz), 5.94 (d, 1 H, J = 4.5 Hz), 7.16 (s, 5 H), 7.33 (s, 5 H), 7.2–7.8 (m, 8 H); FDMS, m/z 737 (M^+ + 1). Anal. Calcd for $C_{37}H_{28}N_4O_3S_5$: C, 60.30; H, 3.83. Found: C, 60.56; H, 3.99.

Reaction of 6 with 5-Mercapto-2-methyl-1,3,4-thiadiazole. To a solution of **6** (72 mg, 0.15 mmol) and 5-mercapto-2-methyl-1,3,4-thiadiazole (37 mg, 2.1 mmol) in *N,N*-dimethylformamido (DMF, 1 mL) was added Et_3N (43 μL, 2.0 mmol) at −10 °C. After being stirred for 1 h the mixture was worked up and chromatographed (SiO_2; benzene–AcOEt, 3:1), affording **7b**: 79 mg, (7[illegible]; colorless foam; IR ($CHCl_3$) 1773, 1716, 1610, 1596 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.66 (s, 3 H), 2.69 (s, 3 H), 3.76 (br s, 2 H), 4.15 (s, 2 H), 4.50 (d, 1 H, J = 14 Hz), 4.67 (d, 1 H, J = 14 Hz), 5.20 (s, 2 H), 5.78 (d, 1 H, J = 4.5 Hz), 5.90 (d, 1 H, J = 4.5 Hz), 7.19 (s, 5 H), 7.31 (s, 5 H); FDMS, m/z 667 (M^+ + 1). Anal. Calcd for $C_{29}H_{26}N_5O_3S_5$: C, 52.23; H, 3.93. Found: C, 52.23; H, 3.75.

Reaction of 6 with Sodium Benzenesulfinate. A solution of **6** (100 mg, 0.21 mmol) and sodium benzenesulfinate (86 mg, 0.52 mmol) in DMF (2 mL) was stirred for 1.5 h at 80 °C. The mixture was worked up and chromatographed (SiO_2; benzene–AcOEt, 8:1) to give **7c**: 87 mg (60%); colorless foam; IR ($CHCl_3$) 1768, 1720, 1606, 1597 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.58 (d, 1 H, J = 16 Hz), 3.85 (d, 1 H, J = 16 Hz), 4.37 (s, 2 H), 4.67 (d, 1 H, J = 14 Hz), 4.81 (d, 1 H, J = 14 Hz), 4.91 (d, 1 H, J = 12 Hz), 4.98 (d, 1 H, J = 12 Hz), 5.63 (d, 1 H, J = 4.5 Hz), 5.82 (d, 1 H, J = 4.5 Hz), 7.1–7.9 (m, 20 H). Anal. Calcd for $C_{35}H_{30}N_2O_7S_3$: C, 61.20; H, 4.40. Found: C, 60.96; H, 4.51.

Ring Opening of the Thiazoline Moiety of 7 with 2-Benzothiazolesulfenyl Chloride. A solution of **7a** (98 mg, 0.13 mmol) in dioxane (3 mL) and 5% HCl (0.3 mL) was stirred at room temperature for 30 min. To this solution was added a solution of 2-benzothiazolesulfenyl chloride prepared from 2-benzothiazolyl disulfide (106 mg, 0.32 mmol) and Cl_2 (0.8 M Cl_2/CCl_4, 0.4 mL, 0.32 mmol) in dioxane (5 mL). After being stirred for 30 min at room temperature, the mixture was passed through a silica gel column with AcOEt. The eluate was concentrated in vacuo, and the residue was chromatographed (SiO_2; benzene–AcOEt, 2:1) to give **8a**: 93 mg (75%); colorless foam; IR ($CHCl_3$) 3390, 1778, 1712, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.56 (br s, 2 H), 4.68 (d, 1 H, J = 13 Hz), 4.68 (d, 1 H, J = 14 Hz), 4.86 (d, 1 H, J = 14 Hz), 4.90 (d, 1 H, J = 12 Hz), 4.98 (dd, 1 H, J = 5, 8 Hz), 5.08 (d, 1 H, J = 13 Hz), 5.08 (d, 1 H, J = 12 Hz), 5.48 (d, 1 H, J = 5 Hz), 6.62 (d, 1 H, J = 8 Hz), 7.10 (s, 5 H), 7.23 (s, 5 H), 7.0–7.9 (m, 12 H); FDMS, m/z 920 (M^+ + 1). Anal. Calcd for $C_{44}H_{33}N_5O_4S_7$: C, 57.43; H, 3.61. Found: C, 57.58; H, 3.64.

Similarly, the disulfides **8b** and **8c** were prepared from **7b** and **7c** in 80% and 58% yields, respectively. The spectral data are as follows.

Compound **8b**: IR ($CHCl_3$) 3400, 1777, 1717, 1683 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.70 (br s, 6 H), 3.75 (br s, 2 H), 4.50 (d, 1 H, J = 13 Hz), 4.50 (d, 1 H, J = 14 Hz), 4.73 (d, 1 H, J = 13 Hz), 4.87 (d, 1 H, J = 14 Hz), 4.98 (d, 1 H, J = 12 Hz), 5.13 (d, 1 H, J = 12 Hz), 5.4–5.6 (m, 2 H), 7.10 (s, 5 H), 7.1–7.9 (m, 10 H); FDMS, m/z 850 (M^+ + 1). Anal. Calcd for $C_{36}H_{31}N_7O_4S_7$: C, 50.86; H, 3.67. Found: C, 50.92; H, 3.96.

Compound **8c**: IR ($CHCl_3$) 3380, 1777, 1717, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.63 (br s, 2 H), 4.11 (d, 1 H, J = 15 Hz), 4.55–5.14 (m, 5 H), 5.32 (d, 1 H, J = 5 Hz), 5.38 (d, 1 H, J = 14 Hz), 6.57 (d, 1 H, J = 8 Hz), 7.1–8.0 (m, 24 H). Anal. Calcd for $C_{42}H_{35}N_3O_8S_5$: C, 57.98; H, 4.05. Found: C, 58.08; H, 3.91.

Cyclyzation of 8 to 9. To a stirred solution of **8a** (56 mg, 0.06 mmol) in THF (2 mL) was added DBU (20 μL, 0.13 mmol) at −78 °C, and the stirring was continued for 30 min at this temperature. After being quenched with concentrated HCl and diluted with AcOEt, the mixture was worked up and chromatographed (SiO_2; benzene–AcOEt, 20:1) to give **9a** (29 mg, 64%) as a colorless foam (R_f 0.42; benzene–AcOEt, 4:1) and **10a** (4 mg, 9%) as a colorless foam (R_f 0.65; benzene–AcOEt, 4:1).

Compound **9a**: IR ($CHCl_3$) 3380, 1782, 1740, 1675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.37 (br s, 2 H), 4.50 (d, 1 H, J = 14 Hz), 4.85 (d, 1 H, J = 14 Hz), 5.22 (s, 2 H), 5.29 (d, 1 H, J = 4 Hz), 5.60 (dd, 1 H, J = 4, 9 Hz), 5.72 (s, 1 H), 6.48 (d, 1 H, J = 9 Hz), 7.00 (s, 5 H), 7.30 (s, 5 H), 7.1–8.0 (m, 8 H); FDMS, m/z 753 (M^+ + 1). Anal. Calcd for $C_{37}H_{28}N_4O_4S_5$: C, 59.02; H, 3.75. Found: C, 58.92; H, 3.96.

Compound **10a**: IR ($CHCl_3$) 3380, 1789, 1727, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.60 (br s, 2 H), 4.34 (d, 1 H, J = 14 Hz), 4.94 (d, 1 H, J = 14 Hz), 5.23 (d, 1 H, J = 4.5 Hz), 5.34 (s, 2 H), 6.03 (dd, 1 H, J = 4.5, 9 Hz), 6.44 (d, 1 H, J = 9 Hz), 6.67 (s, 1 H), 7.23 (s, 5 H), 7.36 (s, 5 H), 7.1–7.9 (m, 8 H); FDMS, m/z 753 (M^+ + 1). Anal. Calcd for $C_{37}H_{28}N_4O_4S_5$: C, 59.02; H, 3.75. Found: C, 59.07; H, 4.02.

In a similar manner, **9b** and **9c** were prepared from **8b** and **8c** in 51% and 55% yields, respectively. The spectral data are as follows.

Compound **9b** (Y = 2-methyl-1,3,4-thiadiazol-5-ylthio): IR ($CHCl_3$) 3390, 1783, 1746, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.68 (s, 3 H), 2.76 (s, 3 H), 3.54 (br s, 2 H), 4.61 (d, 1 H, J = 13.4 Hz), 4.39 (d, 1 H, J = 13.4 Hz), 5.10 (d, 1 H, J = 4.1 Hz), 5.21 (s, 3 H), 5.54 (dd, 1 H, J = 4.1, 8.1 Hz), 6.28 (d, 1 H, J = 8.1 Hz), 7.26 (s, 5 H), 7.33 (m, 5 H). Anal. Calcd for $C_{29}H_{26}N_6O_4S_5$: C, 51.01; H, 3.84. Found: C, 50.92; H, 3.63.

Compound **9c** (Y = SO_2Ph): IR ($CHCl_3$) 3370, 1789, 1722, 1683 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.63 (br s, 2 H), 4.77 (d, 1 H, J = 14.4 Hz), 5.05 (s, 2 H), 5.22 (d, 1 H, J = 14.4 Hz), 5.7–5.9 (m, 2 H), 5.90 (s, 1 H), 7.26 (s, 5 H), 7.2–8.1 (m, 16 H). Anal. Calcd for $C_{35}H_{30}N_2O_8S_3$: C, 59.81; H, 4.30. Found: C, 59.74; H, 4.41.

Registry No. **1**, 86832-59-9; **2**, 86832-60-2; **3**, 86832-61-3; **4**, 86832-62-4; **5**, 86833-34-3; **6**, 86832-63-5; **7a**, 86766-47-4; **7b**, 86766-48-5; **7c**, 86766-49-6; **8a**, 86766-50-9; **8b**, 86784-84-1; **8c**, 86766-51-0; **9a**, 86766-52-1; **9b**, 86766-53-2; **9c**, 86766-54-3; **10a**, 86784-85-2; sodium 2-benzothiazolethiolate, 2492-26-4; 5-mercapto-2-methyl-1,3,4-thiadiazole, 29490-19-5; sodium benzenesulfinate, 873-55-2; 2-benzothiazolesulfenyl chloride, 33405-92-4.

Reaction of Methyl 4-Bromocrotonate with Lithium Ester Enolates: Direct S_N2 Displacement vs. Michael-Initiated Ring Closure

Pirote Prempree, Shuleewan Radviroongit, and Yodhathai Thebtaranonth*

Department of Chemistry, Faculty of Science, Mahidol University, Bangkok 10400, Thailand

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Nucleophilic conjugate addition to an α,β-unsaturated carbonyl compound producing an enolate which subsequently undergoes an intramolecular ring closure has made a considerable impact on organic synthesis strategies.[1] This type of reaction has been termed MIRC (Michael-initiated ring closure) by Little, who showed that three- and five- to seven-membered carbocycles can be formed by this method.[2]

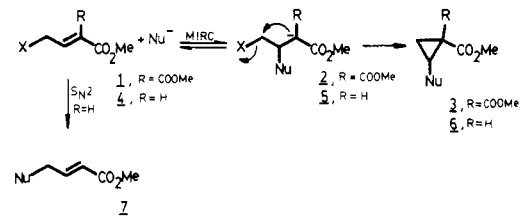
Thus the diester **1** was found to smoothly undergo the MIRC-type of reaction to give **3**[3] and the reaction was

(1) (a) Posner, G. H.; Mallamo, J. P.; Black, A. Y. *Tetrahedron* **1981**, *37*, 3921. (b) Cooke, M. P., Jr. *Tetrahedron Lett.* **1979**, 2199. (c) Chang, Y. H.; Pinnick, H. W. *J. Org. Chem.* **1978**, *43*, 373. (d) Posner, G. H.; Sterling, J. J.; Whitten, C. E.; Lentz, C. M.; Brunelle, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 107.

(2) Little, R. D.; Dawson, J. R. *Tetrahedron Lett.* **1980**, *21*, 2609.

(3) (a) Kolsaker, P.; Storesund, H. J. *J. Chem. Soc., Chem. Commun.* **1972**, 375. (b) Torii, S.; Tanaka, H.; Nagai, Y. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2825. (c) De Vos, M. J.; Krief, A. *Tetrahedron Lett.* **1979**, 1891. (d) Verhe, R.; Courtheyn, D.; De Kimpe, N.; De Buyck, L.; Thierie, R.; Van Caenegem, L.; Schamp, N. *Org. Prep. Proced. Int.* **1981**, *13*, 13. (e) Nugent, S. T.; Baizer, M. M.; Little, R. D. *Tetrahedron Lett.* **1982**, *23*, 1339.

0022-3263/83/1948-3553$01.50/0



successfully applied to the synthesis of pyrethroid acids.[4] However, the cyclopropanation of **4** was almost always accompanied by some direct S_N2 displacement to give, apart from **6**, the product **7**.[2,5] Furthermore, the malonate nucleophile, a reasonably stable anion, was found to react with **4** to give only **7** without any MIRC product being observed.[6]

These facts led to the proposal of a reaction mechanism which suggests that the ratio of the products **6** and **7** depends on the relative stabilities of the nucleophile (Nu^-) and the intermediate **5**, as well as the rate of ring closure (**5** → **6**).[2]

The study of the reaction between methyl 4-bromocrotonate **4** and methyl mercaptide has further indicated that both the solvent and mercaptide gegenion exert remarkable effects on the course of the reaction,[7] and we now present an examination, never before reported, of the reaction of methyl 4-bromocrotonate with various lithium ester enolates in THF and THF/HMPA solvent systems.[8]

Results and Discussion

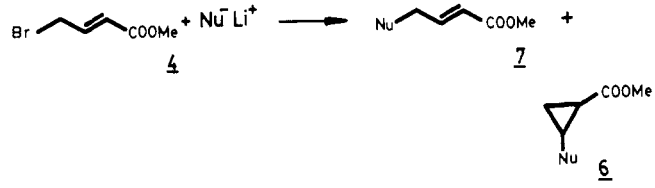
Methyl 4-bromocrotonate was allowed to react with an equimolar lithium ester enolate ($R^- Li^+$) at −78 °C in THF or a THF/HMPA (20/1) solvent system (10 mL of solvent for 1 mmol of reactant), the resulting mixture was left stirring at room temperature for 12 h, and then the reaction was worked up with saturated ammonium chloride solution. Products were obtained which were separated by preparative TLC, and the results are summarized in Table I.

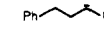
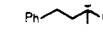
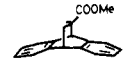
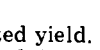
The reaction of methyl 4-bromocrotonate with the malonate anion[6] and the cyclic 1,3-diester anion (entries **a** and **b**) in a THF/HMPA (20/1) solvent system yielded only the products from direct displacement. Similar results were obtained with the nucleophiles derived from methyl phenylacetates (entries **c** and **d**). However, when more reactive nucleophiles were employed, MIRC products became predominant (entries **e**–**h**).

Rather interestingly, when the reactions were carried out in the absence of HMPA the situation became markedly changed. Thus, MIRC products, previously not observed, were now obtained as major products in entries **c** and **d**, while in entries **e**–**i** they were obtained as the sole products.[9]

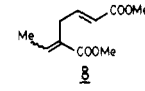
The results appear to agree well with the proposed mechanism for the MIRC reaction where the more stable lithium ester enolates react preferentially via a direct S_N2 displacement while the more reactive enolates undergo an MIRC-type of reaction to give cyclopropanes. Also, without a metal solvating agent (i.e., HMPA) the nucleophile generally reacts at the β-carbon of the crotonate in a Michael addition fashion while the displacement at the γ-position is the preferred mode in the presence of a good metal coordinating solvent.[10]

Table I



compd	Nu^-	20/1 THF/HMPA % 7[a]	20/1 THF/HMPA % 6[a,b]	THF % 7[a]	THF % 6[a,b]
a		31		42	
b		41		complex mixture[c]	
c		66		14	48
d		60		7	62
e		10	54		54
f		17	71		73
g		9	36		58
h			22		73
i	$^-CH_2COOEt$	complex mixture			37
j		*d*		*e*	*e*

[a] Isolated yield. [b] The stereochemistry of **6** not determined; it was presumably a mixture of stereoisomers. [c] White precipitate resulted upon addition of 2,2,5-trimethyl-1,3-dioxane-4,6-dione to the LDA solution and did not change in appearance when methyl 4-bromocrotonate was introduced. The usual workup yielded a large amount of unchanged crotonate together with several minor components. [d] Compound **8** (55%), apparently arising from a direct S_N2 displacement by the dienolate at the α-position followed by a double bond isomerization, was the only product isolated from this reaction. [e] This reaction was not investigated since LDA, the base used throughout the study, adds conjugatively to methyl cortonate in pure THF instead of abstracting a proton to form the required enolate.[11]



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(4) For review see: Arit, D.; Jautelat, M.; Lantzsch, R. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 703.

(5) Ghera, E.; Ben-David, Y. *Tetrahedron Lett.* **1979**, 4603. However, reaction of **1** (X = Br) with phenylmagnesium bromide followed by hydrolysis was reported to give *trans*-2-phenylcyclopropane carboxylic acid as the only product isolated in 13% yield (Ratney, R. S.; English, J., Jr. *J. Org. Chem.* **1960**, *25*, 2213).

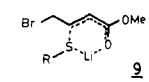
(6) (a) Colonge, P.; Cayrel, J. P. *Bull. Soc. Chim. Fr.* **1965**, *12*, 3596. (b) Kato, T.; Chiba, T.; Sato, H.; Ito, T. *Heterocycles* **1977**, *8*, 417.

(7) Little, R. D.; Dawson, J. R. *J. Am. Chem. Soc.* **1978**, *100*, 4607.

(8) Scattered examples have appeared in the literature where sulfur-, sulfoxide-, and sulfone-stabilized carbanions,[5] Grignard reagent (Ratney, R. S.; English, J., Jr. *J. Org. Chem.* **1960**, *25*, 2213), hydride,[3d] cyanide and alkoxide,[3a,c] sulfide and alkyllithium,[1b,2] and organocuprate[1d] were employed as nucleophiles.

(9) NMR spectra of the crude products (entries e–h) indicated the absence of product **7**.

(10) In the study of the reaction between metal mercaptide and methyl 4-bromocrotonate, Little[7] proposed that in the absence of a metal solvating reagent the lithium metal is coordinated both with sulfur and the ester carbonyl to give a complex (i.e., **9**) in which the nucleophilic sulfur atom is in close proximity to the β-carbon atom of the crotonate, hence induces the Michael attack.



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(11) Herrmann, J. L.; Kieczykowski, G. R.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 2433.

This observation not only provides good supporting evidence for the mechanism of the MIRC reaction, but it is also very useful synthetically, since the appropriate choice of reaction conditions leading to cyclopropane **6** or the substituted crotonate **7** can be made.

Experimental Section

Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR 20A spectrophotometer. ^{1}H NMR spectra were recorded on a Varian EM-360L spectrometer. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane (internal standard). Mass spectra were recorded on a Du Pont 21-490B GC/MS instrument. THF was distilled from sodium/benzophenone ketyl, and hexamethylphosphoric triamide (HMPA) was distilled from calcium hydride and then stored under nitrogen. The molarity of *n*-butyllithium in hexane (purchased from Metallgesellschaft) was determined by titration according to the double-titration method[12] and the diphenylacetic acid method.[13] Reactions were conducted under a nitrogen atmosphere, and reagents were introduced into the flasks via nitrogen-flushed syringes. Unless stated otherwise, products were separated and/or purified by preparative layer chromatography (silica gel, E. Merck) with 6% ethyl acetate in hexane as the eluent in all cases.

General Method. THF Solvent System. Lithium diisopropylamide (LDA; 6 mmol in THF, 40 mL) was prepared in a 100-mL round-bottomed flask equipped with a magnetic bar, a three-way stopcock with a serum cap, and a nitrogen inlet. The solution was cooled to −78 °C, and dimethyl malonate (660 mg, 5 mmol) in THF (5 mL) was introduced via syringe. The reaction temperature was raised to 0 °C for 30 min and then again cooled to −78 °C, and the solution of methyl 4-bromocrotonate (980 mg, 5.5 mmol) in THF (5 mL) was added. The reaction temperature was raised to room temperature and kept there overnight with stirring. After the reaction was quenched with saturated ammonium chloride solution (15 mL), the crude product was extracted into methylene chloride (5 × 10 mL). The solution was washed with water and saturated sodium chloride solution, dried ($MgSO_4$), filtered, and evaporated to dryness. **7a**[6] (480 mg, 42%) was obtained by bulb to bulb distillation as a colorless liquid: IR (film) 1750, 1730, 1720, 1655, 1435, 1270, 1155 cm^{-1}; ^{1}H NMR (CCl_4) δ 2.70 (t, J = 7 Hz, 2 H), 3.42 (dd, J = 8, 7 Hz, 1 H), 3.66 (s, 3 H), 3.72 (s, 6 H), 5.77 (dt, J = 15, 1 Hz, 1 H), 6.77 (dt, J =15, 7 Hz, 1 H); mass spectrum, m/e (relative intensity) 230 (0.5), 198 (38), 166 (100), 139 (38), 111 (94). Anal. Calcd for $C_{10}H_{14}O_6$: C, 52.17; H, 6.13. Found: C, 51.99; H, 6.41.

THF/HMPA (20/1) Solvent System. The procedure was identical with that already explained except that HMPA (2.5 mL) was added to the LDA solution at −78 °C before the introduction of dimethyl malonate. Bulb to bulb distillation of the crude product yielded 350 mg (31%) of **7a**.

2,2,5-Trimethyl-5-(3-carbomethoxy-2-propenyl)-1,3-dioxane-4,6-dione (7b): colorless cubes; mp 59–61 °C (from ether–hexane); IR (Nujol) 1765, 1740, 1720, 1665, 1260, 1200 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.60 (s, 3 H), 1.66 (s, 3 H), 1.70 (s, 3 H), 2.77 (dd, J = 8, 1 Hz, 2 H), 3.66 (s, 3 H), 5.73 (dt, J = 15, 1 Hz, 1 H), 6.61 (dt, J = 15, 8 Hz, 1 H); mass spectrum, m/e (relative intensity) 256 (0.7), 241 (2), 198 (21), 111 (70), 98 (81), 95 (58), 94 (100). Anal. Calcd for $C_{12}H_{16}O_6$: C, 56.25; H, 6.29. Found: C, 56.21; H, 6.38.

Methyl 2-phenyl-2-(2-carbomethoxycyclopropyl)ethanoate (6c): colorless oil; IR (film) 1735, 1725, 1265 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.53–2.40 (m, 4 H), 3.03 and 3.01 (2 d, both J = 9 Hz, 1 H, probably due to two isomers), 3.60 (s, 3 H), 7.22 (s, 5 H); mass spectrum, m/e (relative intesity) 248 (45), 216 (100), 189 (48), 184 (55), 162 (19), 157 (86), 149 (41), 136 (45), 99 (91), 77 (50). Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.62; H, 6.73.

Dimethyl 5-phenyl-2-hexenedioate (7c): colorless oil; IR (film) 1735, 1725, 1655, 1265, 1155 cm^{-1}; ^{1}H NMR (CCl_4) δ 2.30–3.23 (m, 2 H), 3.62 (apparent t, obscured by OMe absorption, J = 7 Hz, 1 H), 3.62 (s, 6 H), 5.71 (dt, J = 16, 1 Hz, 1 H), 6.74 (dt, J = 16 Hz, 1 H), 7.23 (s, 5 H); mass spectrum, m/e (relative intensity) 248 (6), 216 (100), 189 (37), 184 (30), 156 (54), 149 (60). Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 68.01; H, 6.65.

Methyl 2-phenyl-2-(2-carbomethoxycyclopropyl)-propanoate (6d): colorless oil; IR (film) 1740, 1725, 1245, 1170 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.63–1.56 (m, 3 H), 1.36 (s, 3 H), 2.03 (m, 1 H), 3.63 (s, 6 H), 7.19 (s, 5 H); mass spectrum, m/e (relative intensity) 262 (18), 230 (18), 202 (41), 176 (23), 171 (23), 143 (100), 77 (18). Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92. Found: C, 68.52; H, 7.13.

Dimethyl 5-methyl-5-phenyl-2-hexenedioate (7d): colorless oil; IR (film) 1740, 1725, 1655, 1270, 1160 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.55 (s, 3 H), 2.79 (dd, J = 7, 1 Hz, 2 H), 3.63 (s, 6 H), 5.70 (dt, J =15, 1 Hz, 1 H), 6.66 (dt, J = 15, 7 Hz, 1 H), 7.25 (s, 5 H); mass spectrum, m/e (relative intensity) 262 (5.5), 230 (36), 202 (63), 171 (15), 163 (100), 143 (50), 77 (11). Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92. Found: C, 68.44; H, 7.08.

Methyl 2-(2-carbomethoxycyclopropyl)-4-phenylbutanoate (6e): colorless viscous oil; IR (film) 1735, 1725, 1270, 1165 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.76–2.13 (m, 6 H), 2.50–2.80 (m, 3 H), 3.65 (s, 3 H), 3.69 (s, 3 H), 7.19 (s, 5 H); mass spectrum, m/e (relative intensity) 276 (6.5), 244 (15), 216 (16), 190 (16), 184 (16), 172 (32), 158 (20), 140 (100), 104 (65), 91 (71). Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30. Found: C, 69.30; H, 7.42.

Methyl 5-carbomethoxy-7-phenyl-2-heptenoate (7e): colorless viscous oil; IR (film) 1740, 1730, 1660, 1265, 1200, 1160 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.33–2.70 (m, 7 H), 3.64 (s, 6 H), 5.70 (dt, J = 15, 1 Hz, 1 H), 6.61 (dt, J = 15, 7 Hz, 1 H), 7.11 (s, 5 H); mass spectrum, m/e (relative intensity) 276 (2.5), 244 (64), 216 (46), 213 (18), 185 (46), 172 (100), 77 (18). Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30. Found: C, 69.24; H, 7.59.

Methyl 4-phenyl-2-methyl-2-(2-carbomethoxycyclopropyl)butanoate (6f): pale yellow liquid; IR (film) 1735, 1725, 1250, 1170 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.84–1.21 (m, 2 H), 1.06 (s, 3 H), 1.46–2.28 (m, 4 H), 2.44–2.70 (m, 2 H), 3.61 (s, 3 H), 3.64 (s, 3 H), 7.10 (s, 5 H); mass spectrum, m/e (relative intensity) 290 (2), 259 (2), 258 (3), 186 (31), 154 (82), 91 (100). Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.06; H, 7.87.

Methyl 5-carbomethoxy-5-methyl-7-phenyl-2-heptenoate (7f): pale yellow liquid; IR (film) 1735, 1725, 1660, 1200, 1170 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.22 (s, 3 H), 1.62–2.02 (m, 2 H), 2.22–2.72 (m, 4 H), 3.67 (s, 6 H), 5.75 (dt, J = 15, 1 Hz, 1 H), 6.79 (dt, J = 15, 7 Hz, 1 H), 7.12 (s, 5 H); mass spectrum, m/e (relative intensity 290 (0.5), 258 (18), 231 (4), 227 (11), 186 (61), 154 (79), 131 (25), 126 (34), 122 (61) 91 (100). Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.14; H, 7.55.

Methyl 11-(2-carbomethoxycyclopropyl)-9,10-dihydro-9,10-ethanoanthracene-11-carboxylate (6g): colorless prisms; mp 147–148 °C (methylene chloride–hexane); IR (Nujol) 1740, 1720, 1280, 1165 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.06–0.30 (m, 1 H), 0.65–0.98 (m, 1 H), 1.25–1.72 (m, 2 H), 1.26 (dd, J = 13, 3 Hz, 1 H), 2.48 (dd, J = 13, 3 Hz, 1 H), 3.45 (s, 3 H), 3.56 (s, 3 H), 4.20 (t, J = 3 Hz, 1 H), 4.58 (s, 1 H), 6.88–7.32 (m, 8 H); mass spectrum, m/e (relative intensity) 362 (3), 331 (7), 243 (7), 178 (100). Anal. Calcd for $C_{23}H_{22}O_4$: C, 76.22; H, 6.12. Found: C, 76.26; H, 6.19.

Methyl 11-(3-carbomethoxy-2-propenyl)-9,10-dihydro-9,10-ethanoanthracene-11-carboxylate (7g): colorless prisms; mp 142–144 °C (methylene chloride–hexane); IR (Nujol) 1740, 1720, 1655, 1265, 1165 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.49 (dd, J = 12.5, 2.5 Hz, 1 H), 1.88 (ddd, J = 15, 8, 1 Hz, 1 H), 2.51 (ddd, J = 15, 8, 1 Hz, 1 H), 2.71 (dd, J = 12.5, 2.5 Hz, 1 H), 3.50 (s, 3 H), 3.66 (s, 3 H), 4.26 (t, J = 2.5 Hz, 1 H), 4.46 (s, 1 H), 5.64 (dt, J = 15, 1 Hz, 1 H), 6.74 (dt, J = 15, 8 Hz, 1 H), 7.00–7.28 (m, 8 H); mass spectrum, m/e (relative intensity) 362 (1), 303 (3), 243 (0.5), 178 (100). Anal. Calcd for $C_{23}H_{22}O_4$: C, 76.22; H, 6.12. Found: C, 76.05; H, 6.34.

Ethyl 2-methyl-2-(2-carbomethoxycyclopropyl)propanoate (6h): colorless liquid (bulb to bulb distillation); IR (film) 1735, 1725, 1265, 1170 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.07 (s, 6 H), 1.23 (t, J = 7 Hz, 3 H), 0.67–1.75 (m, 4 H), 3.58 (s, 3 H), 4.07 (q, J = 7 Hz, 2 H); mass spectrum, m/e (relative intensity) 214 (3.5), 183 (14), 168 (12), 155 (29), 141 (100), 109 (57). Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.45; H, 8.64.

Methyl 2-(carbethoxymethyl)cyclopropanecarboxylate (6i): colorless liquid (bulb to bulb distillation); IR (film) 1740, 1720, 1170 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.61–0.90 (m, 1 H), 1.05–1.70

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(m, 3 H), 1.26 (t, J = 7 Hz, 3 H), 2.23–2.50 (m, 2 H), 3.65 (s, 3 H), 4.13 (q, J = 7 Hz, 2 H); mass spectrum, m/e (relative intensity) 186 (2.5), 154 (40), 140 (45), 113 (50), 126 (20), 108 (75), 99 (100). Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.79; H, 7.83.

Methyl 5-carbomethoxy-2,5-heptadienoate (8): colorless liquid; IR (film) 1730, 1720, 1660, 1220, 1185 cm^{-1}; ^1H NMR (CCl_4) δ 1.83 (d, J = 7 Hz, 3 H), 3.20 (br d, J = 6 Hz, 2 H), 3.66 (s, 3 H), 3.71 (s, 3 H), 5.68 (dt, J = 16, 1.5 Hz, 1 H), 6.84 (dt, J = 16, 6 Hz, 1 H), 6.96 (q, J = 7 Hz, 1 H); mass spectrum, m/e (relative intensity) 198 (2), 166 (90), 138 (40), 107 (60), 79 (100). Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.60; H, 7.12. Found: C, 60.82; H, 6.93.

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Registry No. **4**, 1117-71-1; **6c**, 86834-71-1; **6d**, 86834-73-3; **6e**, 86846-31-3; **6f**, 86846-32-4; **6g**, 86834-77-7; **6h**, 86834-79-9; **6i**, 86834-80-2; **7a**, 86834-69-7; **7b**, 86834-70-0; **7c**, 86834-72-2; **7d**, 86834-74-4; **7e**, 86834-75-5; **7f**, 86834-76-6; **7g**, 86834-78-8; **8**, 86834-81-3; dimethyl malonate, 108-59-8; dimethyl malonate anion lithium, 74826-01-0; 2,2,5-trimethyl-1,3-dioxane-4,6-dione anion lithium, 71016-33-6; methyl phenylacetate anion lithium, 86834-82-4; methyl 2-phenylpropanoate anion lithium, 86834-83-5; methyl 4-phenylbutyrate anion lithium, 86834-84-6; methyl 2-methyl-4-phenylbutyrate anion lithium, 86834-85-7; methyl 9,10-dihydro-9,10-ethanoanthracene-11-carboxylate anion lithium, 86834-86-8; ethyl 2-methylpropanoate anion lithium, 53807-80-0; ethyl acetate anion lithium, 56267-15-3; methyl 3-butenoate anion lithium, 86834-87-9.

Chiral Syntheses of Protected 3-Amino-4-(alkoxycarbonyl)-2-azetidinones from β-Hydroxyaspartic Acid[1]

Philip G. Mattingly and Marvin J. Miller*[2]

Department of Chemistry, University of Notre Dame, Notre Dame, Indiana 46556

Robin D. G. Cooper and B. W. Daugherty

Lilly Research Laboratories, Eli Lilly and Co., Indianapolis, Indiana 46285

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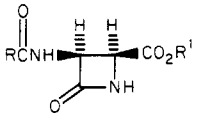
Analogues of the classical β-lactam antibiotics which contain modifications in the core bicyclic or monocyclic ring system are of considerable interest. Several such analogues with improved therapeutic value and resistance to the β-lactamases have recently been obtained from natural sources, by semisyntheses, and by total synthesis. Substituted 3-amino-4-(alkoxycarbonyl)-2-azetidinones **1**



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have been shown to be versatile intermediates for the synthesis of a number of biologically active nuclear analogues of β-lactam antibiotics.[3-5] Although the reported synthesis of **1** is efficient,[3] by design, it can only provide racemic material. Described here is the chiral synthesis of versatile forms of **1** (R = Boc, R^1 = CH_3, C_2H_5).

The planned syntheses (Scheme I) relied heavily on the previously described hydroxamate-mediated ring closure.[6,7] However, the utility of this approach depended on two requirements: (a) the availability of the L-*erythro*-β-hydroxyaspartic acid monoester **4** and (b) the avoidance of the formation of the succinimide derivative **7** observed in related systems.[8,9]

DL-*erythro*-β-Hydroxyaspartic acid has been prepared by conversion of fumaric acid to β-chloromalic acid and subsequent treatment with ammonia.[10] The L isomer was then obtained by resolution.[11] L-*erythro*-β-Hydroxyaspartic acid has also been prepared enzymatically from dihydroxyfumarate.[12] On a more practical scale, the chiral (−)-*trans*-epoxysuccinic acid (**2**) has been treated with ammonia to give L-**3** directly.[13] The epoxide **2** is available from a fermentation broth of *Aspergillus fumigatus* in a yield of over 20 g/L.[14] However, since the fermentation route to **2** was not available to us, the chiral epoxide was prepared from L-tartaric acid by the recently described procedure of Mori and Iwasawa.[15] Thus, diethyl *L*-tartarate was converted to diethyl epoxysuccinate, saponified to the free acid **2**, and subsequently treated with concentrated ammonium hydroxide to give pure crystalline L-*erythro*-β-hydroxyaspartic acid (**3**, Scheme I).

The monomethyl ester **4a** (R^1 = CH_3) was prepared nearly quantitatively by simple, but selective, acid-catalyzed esterification.[16] Reaction with *tert*-butyl pyrocarbonate gave the Boc derivative **5a** which upon coupling with *O*-benzylhydroxylamine gave the desired hydroxamate **6a**. As in the case of hydroxamate methyl esters of malic acid, **6a** was very susceptible to formation of imide **7**.[8] Attempts to purify **6a** by several chromatographic methods resulted in further conversion to imide. Consequently, the crude hydroxamate **6a** was used directly in the azodicarboxylate/triphenylphosphine-mediated cyclization step to provide β-lactam **8a**.

Alternatively, subjection of **4b**, the monoethyl ester of βhydroxyaspartic acid, to the same reaction sequence proceeded without difficulty. During the coupling reaction of the ethyl (*tert*-butoxycarbonyl)-β-hydroxyaspartate **5b** with *O*-benzylhydroxylamine, the hydroxyamate product **6b** precipitated cleanly from the aqueous reaction mixture. No imide was formed even during recrystallization to obtain the analytical sample. Cyclization gave the β-lactam as expected.

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